Evaluation of critically perfused area in acute ischemic stroke for therapeutic reperfusion: A clinical PET study

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To evaluate critically perfused areas in the acute ischemic brain, 9 patients were studied by positron emission tomography (PET) within 7-32 hours after the onset. The cerebral blood flow (CBF) and oxygen metabolic rate (CMRO₂) were evaluated and compared with sequential change in CT findings. In all the regions developing subsequent necrosis on CT, CBF dropped below 17 ml/100 g/min. But in some of these lesions, CMRO₂ remained above the minimum value for regions in which infarction did not develop, and the tissue density on CT obviously remained normal for several hours after PET scan. The mean CBF in these lesions (14.0 ml/100 g/min; range: 9.9-17.3 ml/100 g/min) was significantly higher than that in ischemic areas with low density on CT before or just after PET study (~10 ml/100 g/min; range: 7.7-14.1 ml/100 g/min). These findings suggest that a part of the tissue with CBF between 10-17 ml/100 g/min is still viable at least 7 hours after the onset of ischemia, but becomes non-viable in a longer period of ischemia. These lesions should respond to effective treatment, including therapeutic reperfusion.

Key words: cerebral blood flow, ischemic threshold, cerebral infarction, positron emission tomography

INTRODUCTION

With the recent development of therapeutic intervention and thrombolytic agents such as a tissue-type plasminogen activator, thrombo-embolysis has again seemed to be a feasible therapy in acute ischemic stroke. Indeed, there were some reports that spontaneous recanalization or thrombolytic therapy in the acute period of ischemia produced complete recovery or an improved neurological state. However, inappropriate reperfusion after ischemia may exacerbate brain edema or carry an increased risk of hemorrhagic infarction. Patients who are good candidates for the therapy should be selected to prevent worsening of the patient's condition as much as possible. Although many studies of cerebral blood flow (CBF) subjected to ischemic threshold for infarction in animals and humans have demonstrated that the threshold varies depending on the magnitude of CBF reduction and the duration of ischemic insult, there are only a few clinical PET data on ischemic stroke in the early stages. For this reason, we have reevaluated critically perfused areas in patients with ischemic stroke in its acute phase from the standpoint of CBF and the cerebral oxygen metabolic rate (CMRO₂) by means of positron emission tomography (PET).

SUBJECTS AND METHODS

Patient selection
Nine patients with acute ischemic stroke were re-
Table 1 Neuroradiologic features of the present subjects

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Onset to examination</th>
<th>Laterality</th>
<th>Occlusive lesion on angiogram</th>
<th>Final distribution of infarct on CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>M</td>
<td>CT-1: 2 h CT-2: 9 h PET: 7 h Angio: 0 d</td>
<td>right</td>
<td>MCA (anterior trunk)</td>
<td>Fr-T-P-O, BG.</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>M</td>
<td>CT-1: 7 h CT-2: 30 h PET: 8.5 h Angio: 1 d</td>
<td>left</td>
<td>ICA</td>
<td>Fr-T-P-O, BG.</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>M</td>
<td>CT-1: 4 h CT-2: 10 h PET: 9 h Angio: 0 d</td>
<td>right</td>
<td>MCA</td>
<td>Fr, BG</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>F</td>
<td>CT-1: 2.5 h CT-2: 14 h PET: 11 h Angio: 3 d</td>
<td>left</td>
<td>MCA branches</td>
<td>Fr-T-P-O, BG.</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>M</td>
<td>CT-1: 8 h CT-2: 35 h PET: 13 h Angio: 2 d</td>
<td>left</td>
<td>ICA, MCA (tandem)</td>
<td>Fr-T-P-O, BG.</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>M</td>
<td>CT-1: 15 h CT-2: 19 h PET: 18 h Angio: 1 d</td>
<td>left</td>
<td>No occlusion</td>
<td>Fr-T-P-O, BG.</td>
</tr>
<tr>
<td>7</td>
<td>72</td>
<td>M</td>
<td>CT-1: 23 h CT-2: 10 d PET: 24 h Angio: 10 d</td>
<td>right</td>
<td>No occlusion</td>
<td>T-P</td>
</tr>
<tr>
<td>8</td>
<td>74</td>
<td>M</td>
<td>CT-1: 24 h CT-2: 8 d PET: 26 h Angio: 2 d</td>
<td>left</td>
<td>MCA (anterior trunk)</td>
<td>Fr-T-P-O, BG.</td>
</tr>
<tr>
<td>9</td>
<td>68</td>
<td>F</td>
<td>CT-1: 31 h CT-2: 52 h PET: 32 h Angio: 1 d</td>
<td>right</td>
<td>MCA (posterior trunk)</td>
<td>T-P</td>
</tr>
</tbody>
</table>

CT-1: last CT before PET study, CT-2: first CT after PET study, Angio: angiography, h: hours, d: days, M: male, F: female, ICA: internal carotid artery, MCA: middle cerebral artery, Fr: frontal, T: temporal, P: parietal, O: occipital, BG: basal ganglia

Prospectively selected according to the following criteria.

a) Patients presented with neurological deficit of sudden onset which corresponded to the carotid territory.
b) Patients have no history of cerebral infarction before this insult.
c) PET measurements of CBF and CMRO₂ were completed within 48 hours after the onset of symptoms.
d) Final distribution of infarction on CT was relatively large (more than 2 cm in longer diameter) with involvement of cerebral cortices.
e) No thrombolytic therapy was performed.

The clinical and neuroradiological data for the selected cases are summarized in Table 1. The patients were 7 males and 2 females, aged from 59 to 76 years old (mean ±SD: 68±5.3 years old). PET studies were performed from 7 to 32 hours after the onset (Seven of the 9 patients were studied within 24 hours). Cerebral angiography was performed in all the patients between 0 and 10 days after the onset. In 2 patients (cases nos. 6 & 7) with no occlusive lesion on angiogram, spontaneous recanalization must have occurred before the examination. Informed consent for a PET study was obtained either from each patient or his/her relative before the study in all the cases.

Data Acquisition

The regional CBF, regional oxygen extraction fraction (OEF) and regional CMRO₂ were measured by PET, using HEADTOME III and the ¹⁵O labeled gas steady state inhalation method. Regional cerebral blood volume (CBV) was obtained by one-minute inhalation of C¹⁵O gas. Overestimation of OEF and CMRO₂ due to intravascular non-extracted ¹⁵O radioactivity was corrected for CBV, based on the method by Lammertsma. Before measuring these physiological variables, a transmission scan was performed for attenuation correction of positron annihilation gamma-rays. Arterial blood sampling for measurement of the ¹⁵O concentration in whole blood and plasma was obtained from the radial artery.

The effective transaxial resolution of HEADTOME III is 10 mm of full width at half maximum (FWHM), and the axial resolution is 12 mm of FWHM. Five tomographic slices were simultaneously obtained with 15 mm spacing from 20 mm above the orbito-mental plane. To accurately adjust the anatomical structures of the PET images to those of the CT images, and to immobilize the head during scanning, we used a thermoplastic face mask with landmarks molded for each patient.

Serial CT scans were carried out by a GE 9800 scanner (General Electric, Milwaukee, WI, USA) to evaluate the sequential change in findings. An initial emergent CT scan was carried out at 10 mm thickness with 10 mm intervals about 15 degrees cranial to the orbito-mental plane according to our routine CT study. In all the patients, CT with planes corresponding to PET images were also obtained using the thermoplastic face mask before or after the PET measurement. Intervals between the last CT before the PET and the first one after the PET for cases nos. 7, 8 and 9 were relatively long (Table 1), but in these cases, distribution of low density areas noted before PET studies was similar to the final distribution of infarcts.

Data analysis

Four physiological values, i.e., CBF, CMRO₂, OEF and CBV were obtained simultaneously by means of the image analysis system (VAX-II/750 and DeAnza IP 8500) by setting regions of interest (ROIs) in the reference PET images. Based on the hypothesis that ischemic vulnerability of the middle
cerebral artery (MCA) territory was uniform, about 8 round or elliptic ROIs (12×12 mm–14×40 mm in diameter) were selected in cortical zones of the MCA territory in an affected hemisphere in every patient. These ROIs were located several millimeters deep to the brain surface to minimize partial volume averaging of cerebrospinal fluid spaces. So each region include subcortical white matter as well as gray. On the basis of the sequential changes in serial CT findings, the regions were divided into following four groups:

- **LD-B**: low density (LD) on CT before PET study
- **LD-S**: normodensity on the last CT before PET measurement but LD just after the PET scan, i.e. LD which appeared soon
- **LD-L**: normodensity at least a few hours after the PET scan but finally becoming LD, i.e. LD which appeared later
- **ND**: normodensity throughout the observation

In judging the CT findings, we took into account not only the decrease in tissue density as 'low density' but also effacement of the cortical sulci and obscuration of the corticomедullary junction. To decrease the partial volume effect from surrounding tissues, we discarded the data from the ROI defined in the border of these categories. Statistical difference was examined by one-way analysis of variance with Scheffe's ranging test for multiple comparison, or by Kruskall-Wallis non-parametric analysis. An α of 0.05 was used to determine statistical significance.

**RESULTS**

Figure 1 shows the relationship between CBF and CMRO₂ for every ROI in the groups formed on the basis of the CT findings. In nine LD-B regions in the two patients without an occlusion on the angiogram (cases nos. 6 & 7), CMRO₂ was lower against the higher blood flow. The OEF values for these regions were all below 0.30 (mean±SD: 0.21±0.06). As the mean normal OEF value obtained in our previous PET study was 0.42±0.05 (mean±SD), these LD-B regions are considered to be in a state of luxury perfusion. The regions with luxury perfusion did not include the LD-S and LD-L groups. The oxygen metabolic rate for all the regions in which normodensity was obviously maintained on CT during PET measurement (ND & LD-L) was above 1.6 ml/100 g/min. Except for LD-B areas with luxury perfusion, CBF in the regions of low density or becoming low in density (LD-B, LD-S and LD-L) was below 17 ml/100 g/min.

Table 2 shows the mean values and ranges of CBF, CMRO₂ and OEF for 3 groups becoming low in density on CT (LD-B, LDS and LD-L). The data for the regions with luxury perfusion were excluded from this analysis. The mean CBF and CMRO₂ for the LD-L group were significantly higher than those for another two groups (LD-B & LD-S). There was no difference among these three groups in the mean OEF values (p>0.05). Very few overlaps were found between group LD-L and groups LD-B & LD-S in CMRO₂, but there were relatively large overlaps in CBF ranges. The CBF for LD-L regions was above 10 ml/100 g/min in almost all cases, but

![Graph showing relationship between CBF and CMRO² in the affected hemisphere.](image)

**Table 2** Mean values (±SD) of CBF, CMRO₂ and OEF of the three groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>N</th>
<th>CBF (ml/100 g/min)</th>
<th>CMRO₂ (ml/100 g/min)</th>
<th>OEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD-B</td>
<td>15</td>
<td>9.3±1.7 (7.7–13.4)</td>
<td>1.03±0.30 (0.58–1.49)</td>
<td>0.72±0.13 (0.48–0.92)</td>
</tr>
<tr>
<td>LD-S</td>
<td>7</td>
<td>10.5±2.5 (7.8–14.1)</td>
<td>1.31±0.22 (1.05–1.64)</td>
<td>0.79±0.16 (0.56–0.97)</td>
</tr>
<tr>
<td>LD-L</td>
<td>9</td>
<td>13.9±2.8* (9.9–17.3)</td>
<td>1.82±0.19** (1.60–2.21)</td>
<td>0.74±0.14 (0.57–0.91)</td>
</tr>
<tr>
<td>ANOVA</td>
<td></td>
<td>F=12.6 (p=0.0001)</td>
<td>F=29.3 (p=0.0001)</td>
<td>F=0.67 (p&gt;0.05)</td>
</tr>
</tbody>
</table>

(  ): ranges from minimum to maximum, N: number of ROIs
*: p<0.01 vs. group of LD-B, and p<0.05 vs. group of LD-S
**: p<0.01 vs. groups of both LD-B and LD-S (Scheffe's test)
Table 3  Mean intervals from the onset to the PET study of the three groups

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Intervals (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD-B</td>
<td>15</td>
<td>18.6</td>
</tr>
<tr>
<td>LD-S</td>
<td>7</td>
<td>9.6*</td>
</tr>
<tr>
<td>LD-L</td>
<td>9</td>
<td>8.0**</td>
</tr>
</tbody>
</table>

*: p<0.05 vs. LD-B, **: p<0.01 vs. LD-B (multiple contrast using Kruskall-Wallis test)

the CBF of most LD-B regions was below this level.
Table 3 shows mean intervals from the onset to the PET study. The interval for the LD-B group was significantly longer than those for the other two groups, but there was no significant difference between groups of LD-S and LD-L in the intervals.

**DISCUSSION**

In the case of ischemic stroke, the ‘low density’ area on CT defined in our study is thought to be attributable to vasogenic edema and/or possibly to cytotoxic edema. So the regions of LD-B reflect an established infarcted core. The ‘normodensity’ on CT cannot always represent undamaged tissue, but the ND areas should be morphologically intact tissue, which also may include non-functioning ones, because no definite morphological change had occurred throughout the observation. On the other hand, it is difficult to evaluate the viability of the LD-S or LD-L regions only by their CT-normodensity at the PET study. In addition, there was no definite evidence of maintaining normodensity during a PET scan in the LD-S region, because they had already showed hypodensity on CT just after the PET. As the energy production depends on oxidative phosphorylation, CMRO₂ is considered to reflect the activity of tissues somewhat. Powers et al. used PET to study the minimum CBF and CMRO₂ required by the human brain to maintain viability for more than a few hours in 50 subjects with varying degrees of cerebral ischemia. They found that CMRO₂ was an accurate indicator for distinguishing viable from infarcted tissue. According to their results, CMRO₂ less than 1.3 ml/100 g/min was inadequate to sustain tissue viability for a prolonged period. In our results, CMRO₂ of the LD-L region was above 1.6 ml/100 g/min, which was also the minimum CMRO₂ value for ND regions. This suggests that the LD-L regions should include viable tissue.

We found no definite boundary in CBF between viable and non-viable tissues even with the exclusion of the areas with luxury perfusion. But regions with infarction or subsequent necrosis (LD-B, LD-S, LD-L) were distinguished from those escaping irreversible damage (ND) at 17 ml/100 g/min in blood flow. Considering the interval from the onset to the measurement, the LD-B group was studied significantly later than both the LD-S and LD-L groups, but there were no significant difference between latter two groups (LD-S, LD-L) in ischemic duration. The difference in outcome of these two groups (LD-S, LD-L) should therefore be attributed to the magnitude of the initial CBF reduction. In fact, the mean CBF for the LD-L group (14.0 ml/100 g/min, range: 9.9-17.3 ml/100 g/min) was significantly higher than that for the LD-B and LD-S groups (~10 ml/100 g/min, range: 7.7-14.1 ml/100 g/min). These findings suggest that a part of the tissue with CBF between 10 and 17 ml/100 g/min is still viable at least 7 hours after onset of ischemia, but becomes non-viable in a longer period of ischemia.

As we did not measure subsequent changes in CBF, however, we discuss here the possibility that the CBF of the LD-L regions further decreased after the PET study and this additional reduction in flow produced infarction. First of all, we can refer to many studies about ischemic threshold reported by various investigators. Many experimental studies have demonstrated that membranous failure or irreversible damage occurs when CBF is reduced to around 10-12 ml/100 g/min for 2-3 hours, and lower flow was tolerated for a shorter length of time. Infarction also ensued by reducing CBF to the level of 17-18 ml/100 g/min for permanent MCA occlusion. In clinical studies in humans, there are some reports about the relationship between CBF and electroencephalographic (EEG) changes in patients undergoing carotid arterectomy. The operation was performed without clinical deficit in spite of marked EEG change and CBF reduction to 12-15 ml/100 g/min. But the direct cortical responses may be abolished in CBF of 8-10 ml/100 g/min for 50 minutes before infarction occurs. With PET, Baron et al. studied patients with cerebral infarction of 2-38 days after onset, and showed that the CBF threshold for infarction was around 11 ml/100 g/min. Powers et al. measured the minimum CBF level for the viable tissue (~15 ml/100 g/min) and the normal functioning one (19 ml/100 g/min). These results were obtained from subacute to chronic cases more than 48 hours after onset. There is a report of evidence of penumbra in a PET study. Powers et al. studied 4 patients with vasospasm due to subarachnoid hemorrhage. Two of them recovered and had CBF of 15.0 and 16.2 ml/100 g/min, respectively, in comparison to 12.0 and 11.7 ml/100 g/min in the two with no recovery. The CMRO₂ values were 1.34 and 2.60 against 0.72 and 1.66 ml/100 g/min. These reports were fairly consistent with our results.

We can also refer to the PET study by Heiss et al. of subsequent changes in CBF and CMRO₂ in
patients with ischemic stroke. They studied 16 patients within 6–48 hours of onset and again 13–25 days later. They found that CBF and CMRO$_2$ in the core of infarction did not change during the study period. In the peri-infarct tissue, they demonstrated that the progressive derangement of CMRO$_2$ occurred without a concomitant change in CBF or even with some improvement in flow. These results suggest that CBF should not change greatly in ischemic lesions in and around the core of infarction and their metabolism and tissue integrity should progressively deteriorate in the natural course.

In conclusion, our data demonstrate, in the clinical PET study of humans, that some regions with a residual flow as low as 10–17 ml/100 g/min could maintain viability for at least 7 hours after onset, and that these ischemic lesions demonstrate normodensity on CT in the acute phase although they should subsequently develop irreversible morphological changes. These lesions should exhibit the possibility of effective treatment of ischemia including therapeutic reperfusion. In addition, we were able to evaluate the viability of ischemic area by normodensity on CT to some degree without measuring the blood flow or metabolism.

REFERENCES